Peramivir and other Antiviral Treatment Options for Treatment of Influenza in Hospitalized Patients for the 2009-2010 Season

Dr. Phil Peters, MD, LCDR

October 26, 2009

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Coordinator: Welcome and thank you for standing by, all participants are currently in a listen-only mode. During the question and answer session to ask a question, please press star, 1. As a reminder, today's conference is being recorded; if you have any objections, you may disconnect at this time.

I would now like to turn the conference over to your host Mr. Abnnah Forbes. Sir, you may begin.

Abnnah Forbes: Good afternoon and welcome to today's COCA conference call on peramivir and other antiviral treatment options for treatment of influenza in hospitalized patients for the 2009/2010 season. We are very excited to have Lt. Commander Philip Peters, MD, from the Center for Disease Control and Prevention.

We are not using a PowerPoint presentation for this call, and there will be no CEs offered for this presentation. I will now turn the call over to Dr. Peters.

Philip Peters: Thank you very much and thank you everyone for joining us on this call with very short notice. And I would just say that we will continue to engage the clinical community about this topic, and we are tentatively planning for any of your colleagues who might be interested a repeat call where we'll discuss basically the same issues later on this week. And we'll send out updates regarding that.

And we don't have -- there aren't slides that go with this call, but there are some relevant Web documents, so for people who are by their computer with Internet access, if you go to the www.cdc.gov/h1n1flu Web site, there are two documents that I'd like to point your attention to. If you click on there, the green box on the left that says, "Emergency Use Authorization" if you click to that one box then one of the topics that comes up on that - on the Emergency Use Authorization page is peramivir.

And if you click on IV peramivir, that will bring you to a Web page that has all of the relevant documents related to peramivir. And the two that I'd like bring your attention to is there's one document that's just simply called Intravenous peramivir; and if you click on that, it brings you to a Web page that has the title Antiviral Treatment Options including Intravenous peramivir for the Treatment of Influenza and Hospitalized Patients for the 2009/2010 Season.

And that's one of the documents that I'll - that will contain many of the points that I'll make on this call. And if you want to keep that link open or print that page out, it could be a useful reference for the call. The other document is hyperlinked to within the Antiviral Treatment Options including peramivir page. And if you click on any of the - if you click on the first mentioning of Intravenous peramivir, that will bring you to what's called our Fact Sheet for Healthcare Providers for the Emergency Use Authorization of peramivir.

I just wanted to point out those two documents. To give a summary of what we'll discuss on this call, I'm envisioning that we'll talk for approximately 30 to 35 minutes, and I'll review some of the key points related to peramivir and then we'll have times for question and answer. But as you can imagine, that time won't be enough to exhaustively talk about the subject. But those Web documents do go into complete detail about everything that we know about

peramivir. So everything I'm talking about is contained in those Web documents.

To begin this talk, I'll briefly mention some background as to why the Emergency Use Authorization of peramivir was necessary. Second, I'll move into a more formal discussion about peramivir and what data we do know about the drug. And finally, I want to return to CDC's rec - general recommendations that still apply for how to treat influenza in hospitalized patients and try to put what we've just discussed about peramivir into the context of these general recommendations.

So first, as background, the U.S. Food and Drug Administration or FDA has authorized the use of peramivir under what's called an Emergency Use Authorization which you will hear referred to as an EUA. An EUA allows either the use of an unapproved medical product or the unapproved use of a product that has been approved during certain types of emergencies.

And peramivir has been approved by the FDA for use during this public health emergency of the 2009 H1N1 Influenza virus. Peramivir is a - is the neuraminidase inhibitor class of antiviral drugs that can treat influenza. It was developed by a pharmaceutical company call BioCryst. And it is administered intravenously to treat under the terms and conditions of this Emergency Use Authorization to treat certain patients with suspected or confirmed 2009 H1N1 Influenza.

And again, I'll just reiterate that the healthcare provider fact sheet that is on the CDC Web site reviews the information that's available about peramivir safety and efficacy. So as a little more background as to why the Emergency Use Authorization of this particular drug was approved, we have seen with 2009 H1N1 Influenza virus that there's been a wide spectrum of clinical complications, and a significant number of patients have required hospitalization.

An interesting note of epidemiology is that most hospitalized patients with 2009 H1N1 Influenza have actually been children and non-elderly adults compared to what we typically see with seasonal influenza with much higher rates of elderly adults who require hospitalization. Also a high proportion of hospitalized patients have underlying high-risk medical conditions. And this includes pregnancy.

Worldwide, approximately 6% to 25% of hospitalized patients with 2009 H1N1 Influenza have required admission into an intensive care unit. And broadly there are three types of clinical presentations that have been observed. One is a primary viral pneumonia that has resulted in severe gas exchange abnormalities. A second presentation has been invasive bacterial co-infections such as staph aureus infections, strep pneumoniae infection and Group A strep infections which have caused pneumonias and sepsis.

And a third presentation has been a worsening of organ dysfunction in patients who have poor cardiopulmonary reserve to begin with because of their underlying comorbidities. Now, that being said, severe complications have been seen among persons with underlying medical conditions, they've been seen among pregnant women, and they've been seen among previously healthy persons, including previously healthy children and adolescents.

As many of you have probably heard, we have strongly recommended antiviral treatment for any adults or child who is - has 2009 H1N1 Influenza and requires hospitalization. And this recommendation is based on a review of data that continues to be accumulated suggesting that treatment with neuraminidase inhibitors -- and we'll discuss the different neuraminidase inhibitor drugs in a minute -- but treatment with neuraminidase inhibitors has been associated with survival and with less complicated hospital stays in patients in the United States and Mexico who have had the 2009 H1N1 Influenza infection.

Regarding those medications; in the neuraminidase inhibitor class, there are currently two FDA approved neuraminidase inhibitor antiviral medications. And those are oseltamivir known by the brand name of Tamiflu and zanamivir, known the brand name of Relenza. And these are recommended again by CDC for treatment of hospitalized patients with 2009 H1N1 Influenza virus infection.

Oseltamivir is an oral medication. There - although there have not been randomized clinical trials that have looked at the efficacy of either oseltamivir or zanamivir in hospitalized or critically ill patients with influenza infection, there is an accumulating body of data, observational data, that shows that the use of these drugs, and in particular oseltamivir, is associated with survival in both hospitalized and critically ill patients.

Although rare sporadic cases of the 2009 H1N1 virus have been reported that are resistant to oseltamivir, there is no evidence of any ongoing community-wide transmission of oseltamivir resistant viruses and CDC continues to conduct surveillance to monitor that situation. Zanamivir is a orally inhaled neuraminidase inhibitor. It is provided commercially in a disk-inhaler device that can be used in persons greater than 7 years of age.

One point we would mention in respect to this call is that inhaled zanamivir is not designed or intended to be used as a nebulizer or with mechanical ventilator equipment as there is a risk that the lactose carrier that in the diskhaler device can obstruct the proper functioning of mechanical ventilator equipment.

So just with that as a little bit of background as to why the EUA was issued, I would like to now turn our attention to discussing peramivir in detail. Peramivir can be considered under the EUA that's been issued by the FDA by

clinicians if they have read and understood the content of the fact sheet for healthcare providers.

So this call is summarizing a lot of the key details, but if you're prescribing this medication for one of your patients, the expectation is that you have read and understand and agree to all the terms and conditions that are laid out in the fact sheet for healthcare providers. Peramivir is an investigational neuraminidase inhibitor drug; so within the same class of medications as oseltamivir and zanamivir. It is an intravenous formulation; so as I stated, oseltamivir is an oral medication and zanamivir is orally inhaled, so this is an intravenous medication.

And its use is authorized for treating certain hospitalized patients with confirmed or suspected 2009 H1N1 Influenza. Just to reiterate that indicates that its use is not approved for patients who are not hospitalized, and it's also not approved for use with chemoprophylaxis. I would state that it is an investigational drug because it is still being evaluated in Phase III clinical trials.

The fact that it was approved by FDA for the Emergency Use Authorization indicated that there was enough efficacy and safety data to approve for this indication, but there was not safety and efficacy data that it would be fully approved for commercial marketing. Its mechanism of action is similar to other neuraminidase inhibitors. It's a cyclopentane analog that inhibits the neuraminidase enzyme which is needed for the viral particles to be released from an infected cell.

And if you go to the Fact Sheet for Healthcare Providers, there are specific indications for which peramivir use can be authorized. And I'll just walk through those indications with you. But I'm just turning on my Fact Sheet for Healthcare Providers and that information word for word is on Page 7 of that Fact Sheet for Healthcare Provider document.

But for adult patients, its use is authorized for adult patients for whom therapy with an intravenous agent is clinically appropriate based on one or more of the following reasons: one, the patient not responding to either oral or orally inhaled antiviral therapy. Two, drug delivery by a route other than by the intravenous route is not expected to be dependable or feasible.

And just as further clarification, an example could be an individual that has an ileus and so there is an expectation that oral medications could not be given dependably or feasibly.

And finally, the third reason is that the clinician judges that the intravenous route of intravenous therapy is appropriate due to the circumstances of that patient.

In a similar vein, pediatric patients can also - are also authorized to receive this medication when clinicians believe that an intravenous agent is clinically appropriate to treat their infection. And the reasons again should be reviewed by clinicians and is on Page 7 of the Healthcare Provider Fact Sheet.

And now I'd like to discuss the known efficacy data for peramivir. And, again, this presentation will really just scratch the surface of what is contained in the Fact Sheet for Healthcare Providers. And if you - when you look at this document if you turn to Page 25, there's several pages all the way from Page 25 to 22 -- excuse me -- 41 that reviews Phase II, Phase III trials, some of which have been published in the medical literature, some of which have not been published yet.

So there is an opportunity to fully review the data that is available to us and can help you make a decision as to whether this medication is appropriate for your patients. Approximately 1891 persons in clinical trials have received peramivir either as an intravenous agent or as an intramuscular agent. Of that

total number, 478 received a single dose of 600 mg Intravenous peramivir. And we'll get to the dosing in a minute, but 600 mg once per day is the dose that we are recommending.

And I know as I said, most of those patients that received a single dose data on multiple dose administrations is limited. And 33 adult clinical trial subjects have received approximately 600 mg intravenous for five days or more. And we'll discuss the duration that we're recommending as well.

In addition to this data, peramivir has been used under an emergency IND or Investigational New Drug application through the manufacturer. So there is some additional knowledge that has been accumulated through the manufacturer's compassionate use of this product.

Turning back to some of the clinical trials, again, you can review them on Pages 25 to 41, but I will point out that there is one study that compared five days of IV peramivir to oral oseltamivir in non-critically ill hospitalized adults. And this study showed no important differences in recovery. They seemed to have similar outcomes with IV peramivir and oral oseltamivir. Again though, these were non-critically ill hospitalized adults.

An additional study looked at early treatment of outpatients with a single IV doze of peramivir, and that had comparable results to five days of oral oseltamivir treatment; again in adult outpatients. So as you review this efficacy data, we will emphasize that clinical judgment is going to be an important factor in determining which of your hospitalized and clinically ill patients would benefit from this medication.

With the obvious advantage being that it's available in an intravenous formulation. Now I mentioned that the dosing - or I'd talk a little bit more about the dosing. The dose that we are recommending to use for peramivir is 600 mg once a day administered intravenously for five days or ten days. The

full dosing instructions again are in the Fact Sheet for Healthcare Providers. On Page 8 and Page 10, there are recommendations on how to adjust the dose with renal insufficiency like other neuraminidase inhibitors such as oseltamivir, the dose needs to be adjusted with renal insufficiency.

And on Page 9 of that document, the pediatric dosing is provided which depends on the age of the individual patient. The pediatric dosing in based on modeling and is not based on pharmacokinetic studies done in children.

So I want to turn for a moment to adverse events. Commonly reported adverse events with peramivir in clinical trials have been diarrhea, nausea, vomiting, and neutropenia. That being said, we know that when drugs are used more widely than in clinical trials sometimes additional adverse events are observed. And so it is of utmost importance that clinicians be very cognizant of any adverse events that happen in patients that they are treating with peramivir.

Other neuraminidase inhibitors, not peramivir but others, have in clinical use been associated with rare anaphylaxis and serious skin reactions, and a variety of neurologic and behavioral symptoms. These adverse events should also - should be monitored for very carefully with this drug as well, although they have not been seen in clinical trials to date.

A little more detailed information about the adverse events is again provided in a document for healthcare providers. Several events have only been observed in one or several of patients in clinical trials and so it's unclear what the significance of those adverse events are. I - one point I do want to emphasize however that if you decide to use peramivir for your patients, one condition of the use of peramivir is that we will require mandatory reporting of any serious adverse events that are observed that the clinician judges may be related or possibly could be related to the administration of peramivir.

And as a condition of using the peramivir, after you have received the drug and the drug has presumably been administered, you will receive follow-up from, initially by email, asking if any serious adverse events have happened in the patient that you had used the drug for. And if any of these events have happened, there'll be further instructions on how to report the adverse events. The adverse events will be reported via FDA's MedWatch program and on Page 17 of the Fact Sheet for Healthcare Providers, there is detailed information about what adverse events in particular we are requiring reporting and also Web links to the sites on how the adverse events can be reported.

And I don't think I need to emphasize this with any clinicians, but we definitely want to all work together and try to make sure that as we are releasing this drug and using it with the emergency use that if there are any unanticipated adverse events, that we respond to them very quickly and determine if they're related to the medication very quickly.

And so again that is - that will be something that we will work with you, but we'll need your cooperation and help with. So regarding safety for peramivir, these adverse events that we've discussed have primarily been defined in adult patients because the clinical trials have enrolled adult patients. There is some limited compassionate use data on this medication in individuals who are less than 18 years of age, and there has been to my knowledge only one pregnant woman who has received this drug.

So for pregnant women and for children, adolescents less than 18 years of age, we have no pharmacokinetic, no safety, and no efficacy data to guide the use of this medication. So that is not to say that in certain situations you might still judge that this medication is appropriate, but just keep that in mind when you're reviewing the clinical trial data, efficacy data, and adverse event data. This has all been derived in adult patients.

Patients who need special consideration regarding this drug, I mentioned that dose needs to be adjusted with renal insufficiency. So all patients who are receiving this drug should have a reliable measure of their renal function such as a serum creatinine and a creatinine clearance estimation before the drug is delivered and the dose is calculated.

And as we anticipate many patients will be critically ill who receive this medication, their renal function could certainly fluctuate or change while receiving this medication. And so if it does, appropriate dose adjustments would be needed.

The other major category that we would recommend caution with this medication is for patients who have known or suspected resistance to other neuraminidase inhibitors such as oseltamivir and zanamivir. Now we don't know absolutely that viruses that are resistant to oseltamivir and zanamivir will be resistant to this medication, but in vitro data does seem to indicate that the oseltamivir mutation is also associated with a 80-fold reduction in the insusceptibility to peramivir. So we would not recommend the use of this medication in a virus that was suspected to be resistant to a medication such as oseltamivir.

Categories of patients who should not use this drug at all: patients who have a - who have had an allergic reaction to the currently available neuraminidase inhibitors such zanamivir or oseltamivir should not receive this drug. We don't know exactly if - what the cross reactivity would be to those serious allergic reactions, but would not recommend the use of this medication in those patients.

The final issue I think I will discuss about peramivir and then certainly we can have a lot of questions in the Q&A or we can get into more detail about issues that individuals are interested in. I would just like to review as a clinician what would be your responsibilities if you wanted to use peramivir. But first

you need to inform your patients that this drug is being used because it's been authorized for emergency use. It's not an FDA approved drug, it's an FDA authorized drug for emergency use during this 2009 H1N1 pandemic.

The second is that you should obviously just keep in mind that the patient has the option to accept or refuse peramivir and they should be given the choice to receive this medication after they've heard some of the risks and benefits of using it. And it is your responsibility to know what are the risks and benefits of using peramivir as far as they are known and in all of the information that is known is contained in that Fact Sheet for Healthcare Providers that we feel is known to the extent that it should be used to make those decisions.

And I think one I guess final point about peramivir I'll make is that if you order peramivir, there are details about how peramivir would be ordered in those documents. In particular the document that reviews antiviral options including Intravenous peramivir for treating influenza in hospitalized patients. Your ordering information is there and on several other Web sites at CDC.

If you order the medication, it will be in the order as appropriate. It will be shipped from HHS and CDC's strategic national stockpile. And it is - it will be received by the hospital at your pharmacy and then available for use. But in the interim when you're awaiting the shipment of this medication, the patient should still continue to receive antiviral therapy with an available neuraminidase inhibitor.

So we're just reemphasizing that we - if somebody is hospitalized with influenza, they should be treated with an available agent. Even if you've decided that peramivir is the ideal agent for the patient, you should treat them with oseltamivir or zanamivir until the peramivir has been received and the first dose is administered.

We don't recommend treating combined treatment with peramivir and oseltamivir or zanamivir because they have overlapping mechanisms of action. So you are likely not going to get any additional benefit but potentially could have more side effects.

And an issue regarding the dosing is that the dosing that is recommended is either five days for which there is more clinical trial data or ten days in cases where clinicians feel that there is - that the patient is critically ill and will require a longer treatment course.

The decision to go - to treat for longer than five days is really based on clinical judgment and there has been some expert opinion that longer durations of treatment may be indicated in critically ill patients, but that has not been subjected to any clinical trials to demonstrate its efficacy.

So I'm going to stop talking about peramivir for now. And to wrap up just summarize some of CDC's general antiviral treatment recommendations to put the use of peramivir into the context of what else is also available. So the first point of our general recommendations is that empiric therapy should be initiated as early as possible with a neuraminidase inhibitor in any hospitalized patient who has suspected influenza.

Now this is even if it's clinically suspected, even if the 2009 H1N1 virus has not been confirmed by a real-time PC - RTPCR assay, even in situations where it's clinically suspected but a rapid test is negative. Because as we know and have been trying to emphasize, the sensitivity of rapid tests is quite low for 2009 H1N1 Influenza even among hospitalized patients.

So we are recommending early empiric treatment for anyone who is hospitalized with suspected influenza. Now that - now if we consider the critically ill patients, again, as I had mentioned, there is some expert recommendations, although no clinical trial data. But for patients who have

pneumonia or severe lower respiratory tract disease, some experts have recommended higher oseltamivir doses, twice standard dosing or 150 mg twice daily in adults and treating for a longer duration, ten days, instead of the typical five day treatment course with oseltamivir.

And the reasoning for this is that there is potential for decreased (intralabsorption) in critically ill patients and also high and prolonged replication in the lower respiratory tract of critically ill patients. Incubated patients have been administered oral oseltamivir via a nasogastric and oragastric tube. Limited data indicates that -- and by limited data I'm referring to a study that only involved three patients -- indicated that oseltamivir can be well-absorbed in mechanically ventilated patients who are given oseltamivir by a nasogastric tube.

So there is some indication from the published data that oseltamivir perhaps at a higher dose can be administered to critically ill patients. And there in addition is unpublished data that we have heard about from Canada that has also confirmed that standard dosing of oseltamivir can be given by the nasogastric tube in critically ill patients and can be adequately absorbed.

But I would reemphasize that there are again are not clinical trial data that shows that these approaches or one approach or another approach is better than standard dosing. So for example, the twice daily dosing, twice standard dosing, there is not data that shows it is better than the standard dosing.

So to summarize, again, our recommendations are that empiric antiviral treatment with either oral oseltamivir or orally inhaled zanamivir should be administered as early as possible to all persons with suspected or confirmed influenza who require hospitalization. The initiation of this antiviral treatment should not be delayed pending laboratory confirmation of influenza.

As we discussed on this call, intravenous peramivir has not been authorized by the U.S. FDA subject to the Emergency Use Authorization Terms and Conditions. Intravenous peramivir may be appropriate for certain hospitalized patients and critically ill patients if suspected or confirmed 2009 H1N1 Influenza such as patients who are not responding to oral or inhaled antiviral therapy, and patients without a dependable oral or inhaled route of delivery.

Again, for example, patients who are unable to absorb oseltamivir because of ileus or high nasogastric tube output. And finally, clinicians should carefully review the healthcare provider fact sheet on peramivir. This fact sheet includes all of the terms and conditions of use under the EUA and also includes all of the safety and efficacy data regarding peramivir that I've just been able to touch on in this call.

But I think with that we'll stop and if people could - if individuals who have questions could indicate to the operator, we will start taking questions now.

Coordinator: If you would like to ask a question at this time, please press star, 1, you'll be prompted to record your name. To withdraw your question, press star, 2.

Once again, if you would like to ask a question, please press star, 1. Our first question.

Question: Yes, hello. What is the evidence that some patients' morbidity following infection with the Novel A H1N1 virus is actually due to unchecked viral replication? And assuming this does occur, how would a clinician recognize such individuals?

Philip Peters: Thanks for that question. I think I would refer back there - there has been some work done looking at autopsies of individuals who have died from 2009 H1N1, and earlier in the call I presented some of the critically ill patients, some of the more common presentations. And in one presentation that has

been seen at autopsy has been evidence of a severe viral pneumonia without evidence of bacterial co-infection. So there are a variety of reasons why individuals could get severely ill with 2009 H1N1 Influenza, but one of the reasons is a primary viral pneumonia.

And seve- this issue has come up sometimes with clinical calls if an individual is presenting quite late in their course of illness the question arises, you know, commonly is it even worth treating the influenza at this point. They've, you know, they're presenting ten days into their illness, isn't it more likely that it's bacterial co-infections or other systemic inflammatory response problems that are causing the majority of the morbidity in this person.

And I think on an individual basis it could be quite difficult to know how much is the virus contributing at that stage of the infection. But the downside of treating is really minimal because this in the context of critical illness, you know, that you'll see in the intensive care unit, this, the neuraminidase inhibitor medications in general are very well tolerated, oseltamivir is very well tolerated. So the risk of and downside of treating is minimal and in the upside while in your individual patient might be theoretical, it is there, and it's definitely been seen in autopsy studies.

I believe that data I think is going - has not been published in full, but should be published quite soon. So I'm sorry that I don't have the actual - can't cite the actual reference for you right now, but I can tell you that that has been seen on autopsies in 2009 H1N1. So we could take another question.

Coordinator: Yes. Our next question comes.

Question: Hi, can you hear me?

Philip Peters: Yes, go ahead.

Question: Hi, thank you for that talk. I have two questions that sort of dovetail. How soon to you expect to see some improvement with the use of peramivir in acute - in critically ill patients or for that fact in oseltamivir in not so ill patients. And Part 2 is if the patient is not responding to the oseltamivir or zanamivir and that's one of the indications to use peramivir, what guidelines should we use to decide whether it's because there is some resistance and peramivir wouldn't help.

Philip Peters: Okay, thank you for those questions. I think that the first question regarding how quickly should you see improvement is difficult especially with the critically ill patients. And there have been - there definitely have been case reports not just with 2009 H1N1 Influenza but case reports of the Avian H5N1 Influenza and Seasonal Influenza where patients have died on treatment and at the time of death PCR testing was negative for evidence of active viral replication.

So it certainly would be possible that you could be completely appropriately treating your patient, but there could be a bacterial co-infection or the - just the damage that's been done to different organs from such an extreme systemic inflammatory response, it may have set off a cascade that your - that the patient is not able to recover from.

So with peramivir we are -- initially our recommendation is for either five days or ten day courses of treatment. And one thing we ask people to consider is if they are continuing past a five-day treatment course on to a ten-day treatment course, one possibility is to retest for influenza so you have a positive test when you started treatment in some cases. Retest to see if now the PCR test has turned negative or the viral culture test has turned negative in somebody who doesn't seem like they're responding to treatment at all.

And if the - if those tests are still positive despite treatment, that would be somebody that could be more concerned about antiviral resistance. Again, it

wouldn't confirm that they had antiviral resistance, but it would be someone to be more concerned if those tests had become negative I think that would indicate that the treatment was working. Okay, we can take another question.

Coordinator: Okay, our next question.

Question: Well thank you very much for the conference. I have a question about Intravenous zanamivir and why is not included on you Web site as far as the option and why was peramivir chosen over zanamivir, and do you consider IV zanamivir as an option?

Philip Peters: Yes, thank you for that question. That - it fits in I think well with the previous questions. So peramivir was authorized under the EUA and there are two major aspects that peramivir brings to influenza treatment. One is that it's an intravenous agent, so currently available, there are no intravenous agents. So this at least allows an intravenous agent.

The second reason it was approved by EUA is that the body of safety and efficacy data, although not enough to approve it - that the FDA felt it could outright approve this drug for use, it was felt that its body of safety and efficacy data was enough that it could authorize its emergency use.

So zanamivir is mentioned in the document - the shorter document about antiviral treatment options including intravenous peramivir. There is some mention of intravenous zanamivir and the - this medication is in much earlier stages of clinical trials. It is available however through its manufacturer again by a EIND application, so Emergency Investigational New Drug application. And there have been several patients in the U.S. for which there was concern for a potentially oseltamivir resistant virus in which intravenous zanamivir was used on a very limited basis.

The peramivir and zanamivir I, you know, they really would - are two separate issues. So it's not only, you know, one would be approved by EUA and not the other, but I think I would just leave it at that that the body of evidence was - is available at this time that FDA felt there was enough information on safety and efficacy to approve the use of peramivir.

And in whether we see an EUA related to zanamivir, you know, could be a possibility in the future, but I don't know anything about that. But it has been used on a compassionate basis. And in that document we do reference its use in those very particular situations.

And I think just to mention one more thing about the resistance before we move to the next question is that CDC is conducting ongoing surveillance for antiviral resistance. And to date we have only identified nine cases at CDC labs and two additional cases at non-CDC labs of oseltamivir resistance 2009 H1N1 of over 1000 (isolates) that have been tested. So the rate was about .5%.

And in these particular cases, most often they have occurred in individuals who are severely immunosuppressed and are being treated with antivirals, but because of their immunosuppression are not able to completely clear the infection. And has also happened in individuals who were perhaps - were chemoprophylaxed when they actually had an on a - an ongoing infection, and so resistance developed within the context of chemoprophylaxis.

So we do need to be vigilant about resistance, but it has not been a major problem right now. So we don't anticipate that there would be resistance problems to peramivir which seems to have a similar resistance profile to oseltamivir.

Question Cont'd: Thank you.

Philip Peters: Okay. We got another question?

Coordinator: Yes. Our next question.

Question: Yes, I was wondering how you access that Fact Sheet for Healthcare Providers. Where can we get that?

Philip Peters: Okay. Let me pull up -- so if you go to www.cdc.gov/h1n1flu -- all one word, H1N1flu slash EUA, that will take you to a Web page and you'll see peramivir as one of the options that you can click on. And click on peramivir and that has all of our documents including the Fact Sheet for Healthcare Providers which I think is the most important one.

Question Cont'd: Thank you.

Philip Peters: Okay we can take another question.

Coordinator: Okay, our next question.

Question: Hello, thanks for an interesting talk. Have you considered this a good opportunity to get some PK data maybe especially in kids, you know, working it out that if anybody gets the drug that you'd get one or two serum samples?

Philip Peters: I should point out one thing, that is, anyone who is considering this drug an alternative of - an alternative to using the EUA process and requesting the drug from CDC is to enroll your patient in a clinical trial. And so there are clinical trials that are looking at the use of peramivir in hospitalized patients which would include more vigorous monitoring of adverse events and some of which would generate more PK data.

So I think without maybe going into the full details of it, the - when the Emergency Use Authorization is authorized by FDA, there are certain things that they can require such as reporting of adverse events and things that will -

that would alert them that if there is anything happening related to the drug that is unanticipated and serious. But as part of the EUA, the EUA isn't a mechanism to be able to generate data that would be more research and wouldn't benefit that particular patient.

So I think - I would say that is very important and anybody who is interested in using peramivir in the context of a clinical trial, there are options to do that and if you go to www. -- let me just make sure I have the right -- I'm sorry -- let me just make sure I have the right Web site, I'm sorry -- if you go to http://clincialtrials.gov all one word, and then search peramivir, that will bring up all the trials and the phone numbers of the principle investigators for those trials.

By the way there is a possibility to use this drug in a more research setting that will provide more data, that will be very useful for the whole clinical community in the future, but within the context of the Emergency Use Authorization that's something that we can't require people to do.

Question Cont'd: Thank you.

Philip Peters: We got another question?

Coordinator: I show no further questions at this time.

Philip Peters: Okay. Let's - let me just check the time. We have -- I think we have another ten minutes if a - so I'll just give it another minute or two to see if individuals have questions. I think the total number of people on the call because this was very last minute I think is - I think there are certainly a lot of your colleagues etc. that are probably very interested in this topic. So we will have another discussion about peramivir and sort of a general talk about antiviral treatment options.

And we will also post on the COCA call Web site which Abnnah can give you one more time before we leave, link to the two documents that this talk was really based on. So if you have colleagues that are very interested in - if we could enlist your help to forward them these documents as well because they really contain all of the important information about how to order this drug, safety and efficacy data, and how does this drug fit into the context of other antiviral agents we have.

So is there a last question? And if not, I'll turn it back over to Abnnah to wrap up.

Coordinator: We actually did have about six more pop up, so.

Philip Peters: Okay, well why don't we take some questions until the top of the hour and then we'll wrap up.

Coordinator: Okay. Our first question.

Question: Hi, can you hear me all right?

Philip Peters: Yes, go ahead.

Question Cont'd: I think our worst nightmare would be that this gets loose in a NICU. Has anyone yet given this to a very low birth weight infant?

Philip Peters: No, so you're talking about 2009 H1N1 Influenza outbreak within a NICU?

Question Cont'd: Yes.

Philip Peters: So I guess I'll just make two points about that. We have heard of a, not an outbreak but an exposure that took place within a NICU, but I don't believe that there were any cases that resulted from the exposure. And as I know a lot

of clinicians on the line probably work in maybe NICUs themselves or hospital epidemiologists, infection control is really key in keeping people who might be sick with flu from working in these really high-risk settings is definitely extremely important.

And when the vaccine becomes more widely available being able to get it to healthcare workers, especially healthcare workers who are working in such - with such high-risk populations is important. So the use of this drug peramivir has not been used in NICUs to my knowledge.

And I've - and I probably haven't heard of every case that this drug has been used in, but I've reviewed the clinical trial data that summarized in the Fact Sheet for Healthcare Providers. And the company has - BioCryst who produces this drug has been very forthcoming in showing us data from some of their compassionate use authorizations of this drug. And I haven't seen it used there either, so.

Now in a Neonatal Intensive Care Unit if - I will sort of put in a plug for our general antiviral recommendations that we do have recommendations for the use of oseltamivir for children less than 1 year of age. And we are going to be revising those within the next probably two weeks to include some wording about how oseltamivir would be dosed in premature infants who we all know have very low weight, but also have compromised renal function. So there - you know, and that complicates the dosing.

But we're hopeful to have a little more guidance for how to dose oseltamivir in those situations.

Question Cont'd: Thank you.

Philip Peters: We have another question?

Coordinator: Yes, sir, next question is from.

Question: Good afternoon.

Philip Peters: What you need?

Question Cont'd: Yeah, we've noticed some reluctance among clinicians to use empiric antiviral therapy when treating patients that have what would otherwise be considered kind of straightforward evidence of bacterial pneumonia - a classic lobar infiltrate, maybe some sputum or blood cultures are supportive of a bacterial source.

Could you just comment on the role for concurrent antiviral therapy when the initial clinical impression may be a bacterial pneumonia but not otherwise confirmed?

Philip Peters: Yeah, we've certainly heard about a lot of cases where the initial suspicion was bacterial community-acquired pneumonia and then several days into the hospital course the patient was worsening, not getting better, and a diagnose of influenza was made. And currently we don't have recommendations about necessarily treating community-acquired pneumonia for influenza as a routine, but I would say people have brought that up and I think that's an important issues for the clinical community to keep bringing up, professional organizations, etc. as a consideration.

It certainly doesn't' seem - it certainly does not to me -- now this is not a guideline, but seeing if influenza is circulating within your community, if you're seeing cases of influenza when you have patients presenting with what looks like a community acquired pneumonia, there - I think we could definitely say there needs to be consideration as to whether this could be influenza or not.

And if the clinician thinks that influenza is still a possibility, they suspect influenza is still a possibility; in those situations we would recommend treatment. But again we would -- certainly our recommendations would defer to the clinical judgments of the individual to sort of try to put together what's circulating in your community with the - with your clinical experience.

One I think last maybe plug for antiviral therapy though in those situations is that, you know, often we are reluctant to use antibiotics too aggressively because we worry about the fallout such as generating resistance among other bacteria such as C-Diff infections or multidrug-resistant gram-negative bacteria.

The neuraminidase inhibitors only really have activity against influenza viruses, and they don't have a lot of side effects. So if you treat somebody with oseltamivir and they didn't have influenza, you're not generating influenza in the community, you're not -- excuse me -- you're not generating resistance among influenza viruses in the community.

So there is -- I mean, I think when you compare it to the use of antibiotics, you could maybe make even a stronger case for wanting to empirically use antivirals because the downside and the resistance problems are probably actually less severe.

Is there another question?

Coordinator: Yeah

Question: Yes, thank you for that presentation. Just two quick questions, the first one is there was the release of the Presidential Emergency Declaration this week plus the EUA for peramivir, and the question, are these just two temporarily unrelated events that took place? And then the second question is can you talk about the use of peramivir in the pregnant female patient? Thank you.

Philip Peters: Yes, to answer Question 1, those were - they were unrelated. They just happened to happen around the same time. We released the EUA on peramivir Friday afternoon which is not a -- Friday at 8 pm, actually I think on Friday which is obviously not a great time to release it. But the feeling was that we wanted to get this approved and get drug moving as quickly as possible in that it - patients still come in sick over the weekend so we wanted to get it up as quickly as possible. And even without really announcing it at all until this call, we have had several requests and have sent it out to I believe five hospitals so far.

The second question of the use in pregnant women, none of the clinical trials have looked in pregnant women, so there isn't any data regarding safety, efficacy, adverse events, etc., teratogenicity in pregnant women. So there is much less data. I do know of one situation in which a pregnant women - pregnant woman was treated with peramivir so it has happened once in the U.S. But it wasn't in the context of a clinical trial.

And I think we'll take one more question and then we'll wrap up.

Coordinator: Yeah, and that question.

Question: Just a quick question whether there's a charge for the medication.

Philip Peters: No there is no charge for the medication. It's requested -- if the request comes from CDC and then we through a contractor have the medication shipped to the pharmacist of your hospital.

Question Cont'd: Thank you.

Philip Peters: I guess we could do one more, sorry. And a quick one.

Coordinator: Okay, and that's.

Question: Hi. I was wondering with this use of IV only if you have a patient, say they had a high GI output through an NG and that's why you gave the IV, is there any thoughts if you wanted to convert them over to a PO if the patient wanted to leave or had to be transferred?

Philip Peters: Yes, I think we thought there might be more decisions to discontinue peramivir if clinicians were suspecting an adverse event that could be related to the drug. In their clinical judgment the adverse event could be related to peramivir, we would suggest transitioning to another neuraminidase inhibitor.

So I think the - honestly that's not something that I hadn't really thought about, but the mechanisms of action are essentially the same inhibiting the neuraminidase of the influenza virus. So there shouldn't be a problem changing to a - from IV to oral and vice versa as we're recommending people start oseltamivir while their waiting to get the peramivir, there shouldn't be a problem with that turnover either. Thanks.

Okay, well I think I'm going to turn it over to Abnnah who could just kind of repeat where some of this information can be found and wrap up the call for us. Thanks.

Abnnah Forbes: I want to thank our presenter Dr. Peters for providing our listeners with this information. And I would also like to thank our participants for joining us today. In case you didn't get a chance to ask a question, please send an email to coca@cdc.gov. That's C-O-C-A at cdc.gov.

Also in regards to the two documents that Dr. Peters mentioned during this call, they will be posted to the Web site later on this evening. And to access that information would be go to emergency.cdc.gov/coca -- C-O-C-A --

/callininfo.asp. Repeat; emergency.cdc.gov/coca C-O-C-A/callinfo.asp Thank you very much.

Coordinator: Thank you for participating in today's conference call, you may disconnect at this time.

END